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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1633	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

Office Action Summary	Application No.	Applicant(s)	
	09/827,854	ZANNIS ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *claims 83-95, 98-100, 102-114* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *83-95,98-100,102,103,105-110 and 112-114* is/are rejected.

7)☒ Claim(s) *104 and 111* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 7/6/09 was entered.

The examiner acknowledged a brief telephone conversation on 6/30/09 and agreed with the substance of this conversation as stated in Applicant's amendment dated 07/06/2009.

Amended claims 83-95, 98-100, 102-114 are pending in the present application.

Additionally, in light of Applicant's response to Restriction Requirement, filed on March 2, 2009, Applicants elected with traverse an encoded polypeptide consisting of residues 1-185 of SEQ ID NO:2 on the ground that all of the recited species would not place an undue searching burden on the examiner.

Upon further consideration and in light of the prior art applied below, the species restriction requirement set forth on 10/02/2008 was withdrawn.

Accordingly, amended claims 83-95, 98-100, 102-114 are pending in the present application, and they are examined on the merits herein **with he previously elected SEQ ID NO: 15 (apoE3)**. It is noted that **SEQ ID NO: 2 is the mature apoE3 amino acid sequence, while SEQ ID NO: 15 is the apoE3 preproprotein containing its N-terminal signal peptide**.

Specification

The specification is objected because it lacks antecedent for the limitations "1-203" and "1-247" recited specifically in the claims.

Claim Objections

Claim 83 is objected to because of the term "said secreted polypeptide" is not consistently used in independent claim 83 as well as in its dependent claims. Within the same claim 83, the term “said polypeptide” is also recited.

New claim 103 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. This is because the limitation “said polypeptide has fewer than 200 amino acids” is already present in the independent claim 83 from which claim 103 is dependent on.

Claims 98-100, 110-113 are objected because they contain embodiments of non-elected species (e.g., SEQ ID NOs other than the elected SEQ ID NO:15 and SEQ ID NO:2).

New Matter

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 83-88, 90-95, 98-100, 102-103, 105 and 114 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that

the inventor(s), at the time the application was filed, had possession of the claimed invention. ***This is a modified rejection.***

Amended independent claim 83, its dependent claims and claim 114 recite the new limitation "**amino acid residues 1-185 of SEQ ID NO:2 and one or more amino acids 186-259 of SEQ ID NO:2**". As written, the claims encompass the use of a secreted polypeptide consisting of/ comprising **amino acid residues 1-185 of SEQ ID NO:2 and one or more amino acids 186-259 of SEQ ID NO:2 in any combination as long as they are amino acids 186-259 of SEQ ID NO:2**, for example a secreted polypeptide consisting of/comprising amino acid residues 1-185 of SEQ ID NO:2 in contiguous with amino acids 186-200 of SEQ ID NO:2 or in contiguous with amino acids 186, 200 and 258 of SEQ ID NO:2, or in contiguous with amino acids 190, 195, 200, 210 and 233 of SEQ ID NO:2. The specification as originally filed does not provide any written support for a method of lowering cholesterol in a mammal in need thereof as now broadly claimed. Applicants also failed to point out the specific page number and/or line number in the originally filed specification that provides written support for this new limitation in the Amendments filed on 10/3/07 and on 6/30/08.

Therefore, given the lack of sufficient guidance provided by the originally filed specification, it would appear that Applicants did not contemplate or have possession of invention as now claimed at the time the application was filed.

Response to Arguments

Applicants' arguments with respect to the above rejection in the Amendment filed on 6/30/08 (pages 8-10) have been fully considered but they are respectfully not found persuasive.

Applicants argue basically that the specification teaches that the residues 1-185 of apolipoprotein E contain all the determinants required for clearance of lipoprotein remnants, and that the carboxy terminal region influences triglyceride secretion, with specific working examples that fragments in which residues 186-299, 203-299, 230-299 and 260-299 may be removed from full length apolipoprotein E capable of lowering plasma cholesterol levels without causing hypertriglyceridemia, and therefore one of skill in the art readily capable of making the species falling within the claimed invention. Applicants further argue that description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces.

The main issue is still where is the written support in the specification as-filed that at the effective filing date of the present application that Applicants contemplated the use of **numerous species of a secreted polypeptide** consisting of/comprising amino acid residues 1-185 of SEQ ID NO:2 **in contiguous with amino acids 186-200 of SEQ ID NO:2 or in contiguous with amino acids 186, 200 and 258 of SEQ ID NO:2, or in contiguous with amino acids 190, 195, 200, 210 and 233 of SEQ ID NO:2 for examples as clearly encompassed by the scope of the amended claims**? Once again, Applicants failed to point out the specific page number and/or line number in the specification as filed to support the above limitation. The disclosure that fragments in

which residues 186-299, 203-299, 230-299 and 260-299 may be removed from full length apolipoprotein E capable of lowering plasma cholesterol levels without causing hypertriglyceridemia does not provide a written support for such a limitation in the instant amended claims. Moreover, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. Furthermore, Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Claim 110 is still rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons already set forth in the Office action dated 12/28/2007 (pages 4-11). ***The same rejection is restated below.***

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte*

Forman, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The specification teaches by exemplification showing the construction of recombinant adenoviruses expressing secreted apoE4 and various secreted truncated forms of apoE4 (e.g., apoE4-185, apoE4-202, apoE4-229, EpoE4-259). In an apoE-deficient mouse model, the recombinant adenoviruses were injected intravenously through the tail vein and the effects of full-length apoE4 and its various truncated forms on cholesterol and triglyceride homeostasis were evaluated. Applicants showed that an insignificant reduction of the mouse cholesterol level and a severely induced hypertriglyceridemia were observed in apoE-deficient mice treated with full-length apoE4-adenovirus, whereas reduced levels of cholesterol without the induction of hypertriglyceridemia were obtained in animals treated with recombinant adenoviruses expressing the aforementioned truncated forms of apoE4. Applicants further demonstrated that overexpression of either full-length apoE3 or apoE4 is sufficient to induce combined hyperlipedimia (high cholesterol and triglyceride levels) in normal C57BL6 mice, whereas an overexpression of apoE4-202 has no detectable effect on triglyceride levels of the C57BL6 mice.

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the following reasons.

(a) The breadth of the claim

Claim 110 is directed to a method of lowering cholesterol in a mammal in need thereof without inducing hypertriglyceridemia, wherein said mammal expressing a functional low density lipoprotein (LDL) receptor, said method comprising intravascularly administering to said mammal a replication-defective adenoviral vector comprising a nucleic acid encoding amino acids 1-277 of an apoE preprotein of SEQ ID NO: 15 (the elected species containing SEQ ID NO:2).

(b) The state and the unpredictability of the art

The nature of the instant claims falls within the realm of gene therapy. At the effective filing date of the present application (4/6/2000), the state of the gene therapy art was and still remains unpredictable with respect to the attainment of desired therapeutic effects, for this instance lowering the total serum cholesterol level without inducing hypertriglyceridemia in a mammal expressing a functional LDL receptor, as evidenced by the reviews of Verma et al. (Nature 389:239-242, 1997; IDS), Dang et al. (Clin. Cancer Res. 5:471-474, 1999), Romano et al. (Stem Cells 18:19-39, 2000) and Kawashiri et al. (Curr. Control Trials Cardiovasc. Med. 1:120-127, 2000). Dang et al. stated "Although significant progress has been achieved in our understanding of the limitations of gene therapy by suboptimal vectors, host immunological responses to the vectors, and the lack of long term stable expression, the major challenge that limits clinical translation remains in achieving efficient gene delivery to target tissues" (page 474, col. 2, last paragraph). Romano et al. stated "The potential therapeutic applications of gene transfer technology are enormous. However, the effectiveness of gene therapy programs is still questioned" (see abstract), and "Despite the latest

progress reported in the area of vector design, research strategies still have to tackle critically important issues, such as further improvement of gene transfer technology, especially for *in vivo* gene delivery applications, regulation and control of the transgene expression post-cell transduction, and a variety of complex safety matters. These three main issues are to some extent intertwined and pose severe limitations on the applications of gene transfer technology in therapy" (page 21, col. 1, first paragraph). In October 2000, Kawashiri et al. still stated "Somatic gene therapy is a viable approach to the therapy of several lipid disorders for which therapies are currently inadequate" and "The next decade is therefore likely to witness several clinical trials of gene therapy for lipid disorders" (see Conclusion section, page 125). Kypreos et al. (FASEB J. 15:1598-1600, 2001) also stated "One major parameter in successful gene therapy approaches is **gene dosage** and **expression levels**....The inability of the truncated apoE forms that lack all or part of the carboxyl-terminal 260-299 region to induce hypertriglyceridemia, coupled with their intact ability to clear cholesterol, makes them attractive candidates in future gene therapy applications to correct remnant removal disorders" (page 1600, col. 2, last paragraph). Thus, it is clear that at the effective filing date of the present application gene therapy for the treatment of any lipid disorder was still immature and not routine.

Additionally, at the effective filing date of the present application (4/6/2000) although substantial evidence in the prior art as well as the findings of the present invention suggested or indicated that ApoE functioned **to decrease cholesterol while increasing triglyceride levels** (see references cited on page 6, lines 4-25 of the instant

specification), the findings of Tsukamoto et al. (J. Clin. Invest. 100:107-114, 1997; Cited previously) and Kashyap et al. (J. Clin. Invest. 96:1612-1620, 1995) indicated that under their experimental conditions the infection of ApoE-deficient mice with a recombinant adenovirus capable of expressing a mature, full-length human ApoE (299 amino acid residues) resulted in **a reduction in the plasma total cholesterol level without an induction of hypertriglyceridemia**. Thus, at the effective filing date of the present application it was apparent that the biological activity of the ApoE proteins to maintain cholesterol and triglyceride homeostasis *in vivo*, at least in ApoE-deficient mice, was still unpredictable, let alone in any mammal expressing a functional LDL receptor.

The unpredictability of the biological activity of the ApoE proteins to maintain cholesterol and triglyceride homeostasis *in vivo* is further supported by the results of Yoshida et al. (Circulation 104:2820-2825, 2001) that showed that ApoE-deficient mice receiving apoE-/- bone marrow cells that express human apoE3 or apoE2 or apoEcys142 have cholesterol levels increasing with age and the cholesterol levels are not affected by apoE expression (see abstract). Interestingly, the lesion in male apoE3 mice was 40% smaller than that of control mice, while the lesion of apoE2 mice was similar to that of control mice and apoEcys142 mice showed an unexpected and significant increase in lesion size. It is further noted that ApoE2 differs from apoE3 by having a cysteine instead of an arginine at residue 158; and apoEcys142 contains 2 amino acid substitutions: an arginine substitution for cysteine at residue 142 and an arginine for cysteine substitution at residue 112.

(c) The amount of direction or guidance presented

Apart from the exemplification using an apoE-deficient mouse model with recombinant adenoviruses expressing secreted apoE4 or one of the secreted truncated apoE variants apoE4-185, apoE4-202, apoE4-229, EpoE4-259 (**all of these truncated apoE variants lack the carboxyl-terminal 260-299 region**), the instant specification fails to provide sufficient guidance for a skilled artisan on how to lower the total serum cholesterol level without inducing hypertriglyceridemia in a mammal using a replication-defective adenoviral vector encoding amino acids 1-277 of SEQ ID NO:15 as now claimed. The instant specification fails to provide sufficient guidance for a skilled artisan on which modification(s), for example deletion, insertion or substitution, in which combination(s), and at which amino acid residues in the carboxyl-terminal region of a mature, native, human apoE (amino acids 260-299) still possesses the desired property, for this instance lowering the total serum cholesterol level without inducing hypertriglyceridemia in a mammal expressing a functional LDL receptor. Additionally, at the effective filing date of the present application, there was no evidence of record in the present application or in the prior art indicating that an encoded apoE3-277 possesses the ability to lower the total serum cholesterol level without inducing hypertriglyceridemia in a mammal expressing a functional LDL receptor. As is well recognized in the art, any modification (even a "conservative" substitution) to a critical structural region of a protein is likely to significantly alter its functional properties. Guo et al. (PNAS 101:9205-9210, 2004) estimated that only about a third of single amino acid changes would completely inactivate the average protein and increasing the number of substitutions additively increases the probability that the protein would be

inactivated and that specific proteins may be more or less tolerant to changes (see the entire article). Moreover, even one year after the effective filing date of the present application, Applicants still state "**The identification of amino acid residues within the carboxyl terminal region of apoE, which mediate the hypertriglyceridemic effect of apoE, is the subject of ongoing research**" (Kypreos et al., J. Biol. Chem. 276:19778-19786, 2001; page 19785, col. 2, bottom of the first full paragraph). Furthermore, Yoshida et al. (Circulation 104:2820-2825, 2001) demonstrated that a single amino acid substitution between ApoE2 and ApoE3 proteins can have a significant effect in their biological acitivity *in vivo*, let alone for the breadth of the encoded secreted polypeptide to be utilized in the method as claimed.

As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues discussed above, the unpredictability of the gene therapy as well as the relevant art on the biological activity of apoE protein in lowering the total serum cholesterol level without inducing hypertriglyceridemia, and the breadth of the instant claims, it would have required undue experimentation for one skilled in the art to make and use the instant claimed invention.

Response to Arguments

Applicants' arguments with respect to the above rejection in the Amendment filed on 6/30/08 (pages 10-11) have been fully considered but they are respectfully not found persuasive.

Applicants argue basically that the specification clearly teaches that at least amino acids in the 260-299 range can be removed such that the resulting fragments will still retain the desired therapeutic benefits, and that those of skill in the art will be able to modify amino acids within this range, and test the resulting fragments according to the teaching of the present application and to determine whether they have the desired therapeutic properties. Applicants further argue that this would not have required undue experimentation for one skilled in the art.

Once again, the instant specification fails to provide sufficient guidance for a skilled artisan on which modification(s), for example deletion, insertion or substitution, in which combination(s), and at which amino acid residues in the carboxyl-terminal region of a mature, native, human apoE (amino acids 260-299) still possesses the desired property, for this instance lowering the total serum cholesterol level without inducing hypertriglyceridemia in a mammal expressing a functional LDL receptor. Additionally, at the effective filing date of the present application, there was no evidence of record in the present application or in the prior art indicating that an encoded apoE3-277 possesses the ability to lower the total serum cholesterol level without inducing hypertriglyceridemia in a mammal expressing a functional LDL receptor. As is well

recognized in the art, any modification (even a "conservative" substitution) to a critical structural region of a protein is likely to significantly alter its functional properties. Guo et al. (PNAS 101:9205-9210, 2004) estimated that only about a third of single amino acid changes would completely inactivate the average protein and increasing the number of substitutions additively increases the probability that the protein would be inactivated and that specific proteins may be more or less tolerant to changes (see the entire article). Moreover, even one year after the effective filing date of the present application, Applicants still state "**The identification of amino acid residues within the carboxyl terminal region of apoE, which mediate the hypertriglyceridemic effect of apoE, is the subject of ongoing research**" (Kypreos et al., J. Biol. Chem. 276:19778-19786, 2001; page 19785, col. 2, bottom of the first full paragraph). Furthermore, Yoshida et al. (Circulation 104:2820-2825, 2001) demonstrated that a single amino acid substitution between ApoE2 and ApoE3 proteins can have a significant effect in their biological acitivity *in vivo*, let alone for the breadth of the encoded secreted polypeptide to be utilized in the method as claimed. Accordingly, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 112-113 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which

applicant regards as the invention. ***This is a new ground of rejection necessitated by Applicant's amendment.***

A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 112 recites the broad recitation "an amino acid sequence consisting of amino acid residues 1-259 of any one of SEQ ID NOS:1-6" and the claim also recites "with one or more deletions of amino acids 186-259 threof" which is the narrower statement of the range/limitation.

Claim 113 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted element is "a signal peptide" because a secreted polypeptide consisting of amino acid residues 1-185, 1-202, 1-203, 1-229, 1-247 or 1-259" will not be secreted unless it contains a signal peptide.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Amended claims 83-91, 93-95, 98-99, 102-103, 105-109, 112 and 114 are still rejected under 35 U.S.C. 102(b) as being anticipated by McClelland et al (WO 96/14837) as evidenced by Wetterau et al (J. Biol. Chem. 263:6240-6248, 1988) and Breslow et al (J. Biol. Chem. 257:14639-14641, 1982; Cited previously). ***This is a modified rejection.***

McClelland et al discloses at least a gene therapy method for the treatment of hypercholesterolemia, said method comprises intravenous administering (e.g., portal vein injection or peripheral vein injection) a recombinant replication defective adenoviral vector containing a DNA sequence encoding a human apoliporotein E3 or **a fragment of human apoliporotein E3 that is truncated at the C-terminal** (page 4, line 5 continues to line 9 of page 6; page 9, third paragraph) in a mammalian host, including a human host (page 8, last paragraph). **The C-terminal of a human apolipoprotein E3 is made up of amino acid residues 225-299 as evidenced by the teachings of Wetterau et al** (see at least the abstract). Therefore, the encoded human apolipoprotein E3 fragment that is truncated at the C-terminal that is taught by

McClelland et al is an encoded human apolipoprotein E3 fragment that lacks amino acid residues 225-299. Additionally, the DNA sequence encoding human apolipoprotein 3 or its fragment may further include a leader sequence or portion thereof, a secretory signal or portion thereof of the apolipoprotein E gene (page 5, first paragraph). McClelland et al teaches specifically that **a clone having a perfect match with the expected sequence encoding human apoliporotein E3 with the Genbank accession #K00396 was used** (page 11, last sentence of first paragraph). The sequence encoding human apoliporotein E3 with the Genbank accession #K00396 is the same sequence reported by Breslow et al that has 100% sequence identity to SEQ ID NO:15 (SEQ ID NO:2 plus its signal sequence) of the present invention as evidenced by the teachings of Breslow et al. (see at least Fig. 3 and the attached sequence search). It is also noted that McClelland et al also teach the use of other human apoliporotein E isoforms or allelic variants (page 4, fourth and fifth paragraphs). McClelland et al further teaches that hypercholesterolemia is often associated with cardiovascular disease such as atherosclerosis (page 9, second paragraph), and that the method can be used to treat apolipoprotein-deficient animals, including apoE-deficient animals (page 9, last paragraph). McClelland et al also discloses that the reduction of plasma cholesterol concentrations and changes in the plasma lipoprotein distribution was presumably a result of the association of the human apoE protein with both apoB48- and apoB100-remnant lipoprotein particles, thereby increasing removal from the circulation (page 22, last sentence). Please noted that the DNA sequence encoding a fragment of human apolipoprotein E3 that is truncated at the C-terminal taught by McClelland et al also

encodes amino acids 1-203 and/or 1-220 of SEQ ID NO:2; as well as 100% local sequence identity to amino acid residues 1-229 or 1-259 of SEQ ID NO:2 (claims 87-89) or the amino acid sequence of SEQ ID NO:2 (claim 102).

Accordingly, the method taught by McClelland et al has the same method steps and the same starting materials as the instant broadly claimed methods. Therefore, the reference anticipates the instant claims.

Response to Amendment

Applicant's arguments related to the above rejections in the Amendment filed on 6/30/08 (pages 12-14) have been fully considered, but they are respectfully not found persuasive for the reasons discussed below.

Once again, Applicants argue basically that the McClelland et al reference fails to teach or suggest each and every limitation of the instant claims because it only describes generic apolipoprotein E fragments (i.e., those having unspecified deletions at the C-terminus and/or the N-terminus). Applicants highlighted the statement "Such fragments and derivatives of apolipoprotein E retain the same biological activity as unmodified apolipoprotein E" in a paragraph defining the term "fragment or derivative thereof" by McClelland et al. Applicants also argue that the Office improperly uses the Wetterau et al reference to expand the meaning of the term "fragments" as it is used by McClelland et al. to encompass apolipoprotein E fragments not even disclosed or conceived by McClelland et al. Applicants further argue that McClelland et al fails to

teach or suggest even a single species within the broad genus of apolipoprotein E fragments, and thus the use of Wetterau et al reference is an improper use of a secondary reference in making a rejection under 35 USC 102. Moreover, the missing descriptive matter, for this instance apoE fragments lacking amino acids 225-299, is not necessarily present in the disclosure of McClelland et al because McClelland et al failed to describe the apoE fragment disclosed by Wetterau et al, while one of many possibilities, is not necessarily the one described by McClelland et al. Applicants further implied that the McClelland reference is not enabled and that the McClelland's 1995 publication in Exhibit A made no mentioning of "fragments". Applicants further argued that the examiner apparently recognizes the serious deficiencies of the McClelland reference by stating that "the McClelland et al reference **does not teach** explicitly the use of a fragment of human apolipoptorein E3 that is **truncated at the C-terminus or C-terminal end**....Nor does the McClelland et al reference teach the use of **a fragment of a human apolipoprotein E3 that is truncated within the C-terminal**". Finally, Applicants requested that it be shown where the McClelland reference provides an enabling disclosure of each element of the claimed invention, namely methods involving the use of the recited apolipotrotein E fragments for lowering total serum cholesterol without inducing hypertriglyceridemia.

Firstly, the Office has not expanded the meaning of the term "fragments" as it is used by McClelland et al in any shape or form. McClelland et al disclosed clearly at least a gene therapy method for the treatment of hypercholesterolemia, said method comprises intravenous administering (e.g., portal vein injection or peripheral vein

injection) a recombinant replication defective adenoviral vector containing a DNA sequence encoding a human apoliporotein E3 or **a fragment of human apoliporotein E3 that is truncated at the C-terminal** (page 4, line 5 continues to line 9 of page 6; page 9, third paragraph) in a mammalian host, including a human host (page 8, last paragraph). Please note that that the McClelland et al reference **does teach** explicitly the use of a fragment of human apolipoprotein E3 that is truncated **at the C-terminus or C-terminal end**; and this is contrary to Applicant's arguments. The examiner simply relied on the Wetterau et al. reference for what is known in the prior art for the term "the C-terminal of apolipoprotein E3". **"The C-terminal" of a human apolipoprotein E3 is made up of amino acid residues 225-299 as evidenced by the teachings of Wetterau et al** (see at least the abstract). **Therefore, the encoded human apolipoprotein E3 fragment that is truncated at the C-terminal taught by McClelland et al is an encoded human apolipoprotein E3 fragment that lacks amino acid residues 225-299**.

Secondly, such a fragment of human apolipoprotein E3 that is truncated at the C-terminal taught by McClelland et al **would retain the same biological activity as unmodified apolipoprotein E and consistent with the term "fragment or derivative thereof" defined by McClelland et al**. Please note that Tsukamoto et al. (J. Clin. Invest. 100:107-114, 1997; Cited previously) and Kashyap et al. (J. Clin. Invest. 96:1612-1620, 1995) already showed that under their experimental conditions the infection of ApoE-deficient mice with a recombinant adenovirus capable of expressing a

mature, full-length human ApoE (299 amino acid residues) resulted in **a reduction in the plasma total cholesterol level without an induction of hypertriglyceridemia**.

Thirdly, there is no requirement that the cited McClelland et al reference has to provide a working example using a fragment of human apolipoprotein E3 that is truncated at the C-terminal ; or the teachings of McClelland et al should be limited only to working examples as argued by Applicants. The McClelland's 1995 publication in Exhibit A is not relevant to the above rejection because it is not part of the rejection.

Fourthly, it is unclear why the McClelland et al reference is not enabled given the explicit teachings disclosed by McClelland et al as already discussed above. At the effective filing date of the present application, there is nothing unpredictable about the construction of an adenoviral construct encoding a fragment of human apolipoprotein E3 that is truncated at the C-terminal as taught clearly by McClelland et al; and that the use of such a vector construct would result in lowering at least cholesterol in a mammal in need thereof as evidenced at least by numerous prior art of record such as the teachings of Westerlund et al. (J. Biol. Chem. 268:15745-15750, 1993; IDS); Dong et al (J. Biol. Chem. 269:22358-22365, 1994; IDS); Strittmatter et al (US 5,811,243); Tsukamoto et al. (J. Clin. Invest. 100:107-114, 1997; Cited previously) and Kashyap et al. (J. Clin. Invest. 96:1612-1620, 1995) as well as the results of the present application.

Fifthly, with respect to the statements made by the Examiner as cited by Applicants, it appears that Applicants misconstrued the statements made by the examiner in the response to Applicant's arguments despite the explicit teachings of

McClelland et al. Once again, please refer to the teachings of McClelland et al as set forth in the above rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Amended claims 83 and 91-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over McClelland et al (WO 96/14837) as evidenced by Wetterau et al (J. Biol. Chem. 263:6240-6248, 1988), Breslow et al (J. Biol. Chem. 257:14639-14641, 1982; Cited previously) and in view of French et al. (US 6,290,949) for the same reasons already set forth in the Office Action mailed on 5/31/2007 (pages 18-21). ***The same rejection is restated below.***

McClelland et al discloses at least a gene therapy method for the treatment of hypercholesterolemia, said method comprises intravenous administering (e.g., portal vein injection or peripheral vein injection) a recombinant replication defective adenoviral vector containing a DNA sequence encoding a human apoliporotein E3 or **a fragment of human apoliporotein E3 that is truncated at the C-terminal** (page 4, line 5 continues to line 9 of page 6; page 9, third paragraph) in a mammalian host, including a human host (page 8, last paragraph). **The C-terminal of a human apolipoprotein E3 is made up of amino acid residues 225-299 as evidenced by the teachings of Wetterau et al** (see at least the abstract). Therefore, the encoded human apolipoprotein E3 fragment that is truncated at the C-terminal that is taught by McClelland et al is an encoded human apolipoprotein E3 fragment that lacks amino acid residues 225-299. Additionally, the DNA sequence encoding human apolipoprotein 3 or its fragment may further include a leader sequence or portion thereof, a secretory signal or portion thereof of the apolipoprotein E gene (page 5, first paragraph). McClelland et al teaches specifically that **a clone having a perfect match with the expected sequence encoding human apoliporotein E3 with the Genbank accession #K00396 was used** (page 11, last sentence of first paragraph). The sequence encoding human apoliporotein E3 with the Genbank accession #K00396 is the same sequence reported by Breslow et al that has 100% sequence identity to SEQ ID NO:15 (SEQ ID NO:2 plus its signal sequence) of the present invention as evidenced by the teachings of Breslow et al. (see at least Fig. 3 and the attached sequence search). It is also noted that McClelland et al also teach the use of other human apoliporotein E

isoforms or allelic variants (page 4, fourth and fifth paragraphs). McClelland et al further teaches that hypercholesterolemia is often associated with cardiovascular disease such as atherosclerosis (page 9, second paragraph), and that the method can be used to treat apolipoprotein-deficient animals, including apoE-deficient animals (page 9, last paragraph). McClelland et al also discloses that the reduction of plasma cholesterol concentrations and changes in the plasma lipoprotein distribution was presumably a result of the association of the human apoE protein with both apoB48- and apoB100-remnant lipoprotein particles, thereby increasing removal from the circulation (page 22, last sentence).

McClelland et al does not teach specifically to administer the vector to an artery at the site of a lesion.

However, at the effective filing date of the present application, French et al already taught at least of direct intra-arterial injection or infusion of a recombinant replication defective adenoviral vector carrying gene sequences that are capable of ameliorating symptoms of cardiovascular diseases such as atherosclerosis or dyslipidemia or restenosis in a mammal (see at least Summary of the Invention, particularly col. 5; and examples 6-7).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of McClelland et al by also delivering the replication-defective adenoviral vector to an artery at the site of a lesion in a mammal suffering a cardiovascular disease such as atherosclerosis in light of the teachings of French et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because the specific localized gene delivery for ameliorating symptoms of cardiovascular diseases such as atherosclerosis or dyslipidemia or restenosis in a mammal using a recombinant replication defective adenoviral vector has been taught and successfully demonstrated by French et al.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of McClelland et al as evidenced by Wetterau et al, Breslow et al and in view of French et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Amendment

Applicant's arguments related to the above rejections in the Amendment filed on 6/30/08 (pages 14-15) have been fully considered, but they are respectfully not found persuasive for the reasons discussed below. It is noted that Applicants simply restated the arguments made in Applicant's October 11, 2007 Response.

1. Applicants argue that McClelland et al reference is completely silent on the structure and sequence of the generically described apolipoprotein E truncation mutants used to lower cholesterol, the function of these apolipoprotein E truncation Mutants, and on the effect of these generic truncation mutants on triglyceride levels. Applicants also argue that the Wetterau et al reference fails to provide any basis to

conclude that the generic C-terminal apolipoprotein E3 truncation fragment described by McClelland et al is or includes the apolipoprotein E proteolytic fragment consisting of amino acids 1-224, or any of the disclosed fragments of Wetterau et al is biologically active or would retain the biological activity of full length apolipoprotein E3 as required by the methods of McClelland et al., and should be used to treat hypercholesterolemia according to the method of McClelland et al. Neither the Breslow et al reference nor the French et al reference provides remedy for the deficiencies of McClelland et al and/or Wetterau et al. references.

Firstly, McClelland et al disclosed clearly at least a gene therapy method for the treatment of hypercholesterolemia, said method comprises intravenous administering (e.g., portal vein injection or peripheral vein injection) a recombinant replication defective adenoviral vector containing a DNA sequence encoding a human apoliporotein E3 or **a fragment of human apoliporotein E3 that is truncated at the C-terminal** (page 4, line 5 continues to line 9 of page 6; page 9, third paragraph) in a mammalian host, including a human host (page 8, last paragraph). **The examiner simply relied on the Wetterau et al. reference for what is known in the prior art for the term "the C-terminal of apolipoprotein E3". "The C-terminal" of a human apolipoprotein E3 is made up of amino acid residues 225-299 as evidenced by the teachings of Wetterau et al** (see at least the abstract). **Therefore, the encoded human apolipoprotein E3 fragment that is truncated at the C-terminal taught by McClelland et al is an encoded human apolipoprotein E3 fragment that lacks amino acid residues 225-299**.

Secondly, please note that the Wetterau et al and Breslow et al. references were cited as evidence for the teachings of McClelland et al. The only missing teaching in the McClelland et al reference in the above 103 (a) rejection is administering the vector to an artery at the site of a lesion, and this missing embodiment is supplemented by the teachings of French et al. The above rejection also provides motivations why an ordinary skilled artisan would have combine the teachings McClelland et al and French et al. There is no evidence of record indicating or suggesting why an ordinary skilled artisan would doubt that a fragment of human apoliporotein E3 that is truncated at the C-terminal would not lower cholesterol in a mammal in need thereof as clearly taught by McClelland et al.

2. Applicants further argue that Wetterau et al reference teaches away from the use of ApoE proteins having carboxy-terminal truncations because the reference states that apolipoprotein E3 fragments that contain the C-terminal end are more likely to be those that bind to lipoprotein complexes involved in the clearing of cholesterol from the plasma on the basis of the highlighted statements such as "**The precise region or regions of apoE that are the most important for its binding to a lipoprotein surface are not known, although the carboxyl-terminal domain may be a good candidate**", "**[A]lthough the amino terminal domain may have lipid-binding capabilities in certain situations, on very low density lipoprotein the carboxyl-terminal domain of apoE may play an important role in lipid interaction**".

Once again, please note that **the examiner simply relied on the Wetterau et al. reference for what is known in the prior art for the term "the C-terminal of apolipoprotein E3". "The C-terminal" of a human apolipoprotein E3 is made up of amino acid residues 225-299 as evidenced by the teachings of Wetterau et al** (see at least the abstract). Furthermore, there is no "teaching-away" whatsoever by the Wetterau et al reference. The entire reference is on the characterization of human apolipoprotein E3 in aqueous solution, which contains two independently folded structural domains of markedly different stabilities: an amino-terminal domain and a carboxyl-terminal domain, separated by residues that may act as a hinge region (see abstract). **There is no factual evidence indicating that a fragment of human apoliporotein E3 that is truncated at the C-terminal is not capable binding to lipids**. Wetterau et al clearly stated that "Both the isolated model amino- and carboxyl-terminal domains of apoE are capable of binding to dimyristoylphosphatidylcholine (15); thus, **both domains have lipid-binding capabilities**. **The precise region or regions of apoE that are the most important for its binding to a lipoprotein surface are not known**, although the carboxyl-terminal domain **may be a good candidate**" (page 627, col. 1, last paragraph). It is only **a suggestion and not a factual evidence** that the carboxyl-terminal region of apoE **may be a major lipid-binding region**. Even this statement **does not exclude that a fragment of human apolipoprotein E3 that is truncated at the C-terminal is capable of binding to lipids**.

3. Applicants further argue that there is no reasonable expectation of success to use the truncated ApoE of Wetterau et al in the method of McClelland et al as set forth in the above rejection because Wetterau et al directed the skilled artisan away from the use of apolipoprotein E truncation mutants that lack the C-Terminal residues based on the lipid-associating properties of the C-terminal domain of apolipoportein E3.

Please see the Examiner's rebuttals to Applicant's arguments in the preceding paragraphs. McClelland et al disclosed clearly at least a gene therapy method for the treatment of hypercholesterolemia, said method comprises intravenous administering (e.g., portal vein injection or peripheral vein injection) a recombinant replication defective adenoviral vector containing a DNA sequence encoding a human apoliporotein E3 or **a fragment of human apoliporotein E3 that is truncated at the C-terminal** (page 4, line 5 continues to line 9 of page 6; page 9, third paragraph). The results of this application also confirmed the teachings of McClelland et al. Furthermore, **there is no factual evidence indicating that a fragment of human apoliporotein E3 that is truncated at the C-terminal is not capable binding to lipids**. Therefore, an ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of McClelland et al as evidenced by Wetterau et al, Breslow et al and in view of French et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Amended claims 83-91, 94-95, 98-100, 102-103, 185-109, 112 and 114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Strittmatter et al (US 5,811,243) in view of Kahn et al. (US 6,756,523), Breslow et al (J. Biol. Chem. 257:14639-14641, 1982; Cited previously) and Bisgaier et al (US 2002/0188012). ***This is a new ground of rejection.***

Strittmatter et al disclosed at least a method comprising intravenous administering to a subject, including a human, combating Alzheimer's disease or determined to be at risk of developing Alzheimer's disease of afflicted with dementia, any suitable viral vector which carries a nucleic acid encoding ApoE (including ApoE1-ApoE4) or ApoE fragments (e.g., ApoE3 fragments 1-191, 1-244, 1-266 and 1-272) (see at least Summary of the Invention; col. 3, line 52 continues to line 50 of col. 4; col. 5, lines 30-60; col. 6, lines 49-62).

Strittmatter et al does not teach specifically the use of a replication-defective adenoviral vector or ApoE3 having SEQ ID NO:2 to treat a mammal, particularly a mammal in need of lowering cholesterol; even though the reference discloses that any suitable viral vector and any ApoE, including ApoE3 and its fragments can be used.

However, at the effective filing date of the present application, Kahn et al already taught the use of a recombinant replication defective adenovirus vector for the expression of selected nucleotides in the cells of the central nervous system (see at least col. 3, lines 1-54).

Additionally, Breslow et al already cloned a human apolipoprotein E3 cDNA having 100% sequence identity to SEQ ID NO:15 (SEQ ID NO:2 plus its signal

sequence) of the present invention (see at least Fig. 3 and the attached sequence search).

Furthermore, Bisgaier et al also taught specifically clinical studies showed that **total serum or LDL cholesterol was elevated in patients with Alzheimer's disease**, particularly individuals who are ApoEε4 and tend to manifest hypercholesterol; and that epidemiological investigations have further demonstrated that **the risk for AD was greater in individuals with high cholesterol levels, and that the onset of AD occurred earlier in those individuals who were ApoEε4 with high serum cholesterol** (paragraph 5). Bisgaier et al further disclosed a method for treating or preventing the onset of Alzheimer's Disease by administering to a mammal suffering from AD an effective amount of an agent that lowers the mammal's blood triglyceride level and its cholesterol level (see at least Summary of the invention).

Accordingly, it would have been obvious for an ordinary skilled artisan to modify the method of Strittmatter et al by also using a replication defective adenoviral vector containing a DNA sequence encoding ApoE fragments (e.g., ApoE3 fragments 1-191, 1-244, 1-266 and 1-272), including a DNA sequence encoding human ApoE3 fragments obtained from the human cDNA clone taught by Breslow et al. to treat a mammal suffering or at risk of developing AD, particularly individuals who were ApoEε4 with high serum cholesterol, in light of the teachings of Kahn et al., Breslow et al. and Bisgaier et al. as discussed above. Please also note that the adenoviral vector construct must contain a nucleic acid sequence encoding a signal peptide for proper synthesis of the ApoE3 fragments in cells of the treated patients.

An ordinary skilled artisan would have been motivated to carry out the above modifications because Kahn et al already taught various advantages for using a recombinant replication defective adenovirus such as its great efficacy of infection, long term expression, wide host range and low toxicity (col. 3, lines 1-11). Additionally, the human ApoE3 cDNA was already available and cloned in the prior art since 1982. Furthermore, Bisgaier et al already taught that clinical studies showed that total serum or LDL cholesterol was elevated in patients with Alzheimer's disease, particularly individuals who are ApoEε4 and tend to manifest hypercholesterol; and that epidemiological investigations have further demonstrated that the risk for AD was greater in individuals with high cholesterol levels, and that the onset of AD occurred earlier in those individuals who were ApoEε4 with high serum cholesterol. The modified method resulting from the combined teachings of Strittmatter et al., Kahn et al., Breslow et al. and Bisgaier et al. is indistinguishable from the methods as broadly claimed because it has the same method steps and starting materials.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Strittmatter et al., Kahn et al. Breslow et al. and Bisgaier et al., coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusions

No claim is allowed.

Claim 104 objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN/

Primary Examiner, Art Unit 1633